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(54) Title: ENZYMIC ALTERATION OF HAIR GROWTH

(57) Abstract

The rate and character of mammalian hair growth is altered by topical application to the skin of a composition containing a dermatologically acceptable carrier and an inhibitor of S-adenosylmethionine decarboxylase with or without an ornithine decarboxylase inhibitor.

* See back of page

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ENZYMIC ALTERATION OF HAIR GROWTH

This invention relates to alteration in the rate and character of mammalian hair growth by topical application through the skin of compositions containing an inhibitor of the enzyme S-adenosylmethionine decarboxylase.

U.S. Patent No. 4,039,669 describes the topical use of 17-alpha-R-androst-4-en-17-beta-ol-3-one or esters thereof where the R is n-propyl or n-butyl for the control of dermatological systems associated with androgen-mediated conditions such as acne.

U.S. Patent No. 4,139,638 and 4,161,540 describe the use of certain 4'-substituted and 3', 4'-disubstituted anilides for the treatment of androgen dependent disease states such as female hirsutism and acne.

U.S. Patent No. 4,191,775 discloses that certain 3,4-disubstituted branched-chain fluorinated acylanilides may be used in the topical treatment of androgen-dependent disease conditions such as acne, female hirsutism, and seborrhea.

U.S. Patent No. 4,344,941, describes the topical use of certain androgenic 17-alpha- substituted steroids exemplified by 17-beta-hydroxy-1-alpha-methyl-17-alpha(1-methyl-2-propenyl)-5-alpha-androstan-3-one for the treatment of diseases such as acne, seborrhea, alopecia and female hirsutism.

U.S. Patent No. 4,367,227 describes a cosmetic composition for reducing sebum secretion from the skin

comprising alcoholic solutions of cyproterone acetate. West German OLS 2,840,144 describes the use of a combination of progesterone with either cyproterone acetate or chlormadinone acetate in the topical treatment of androgen induced hormonal disturbances such as alopecia, female hirsutism, and acne.

Japanese Kokai 58-57308 describes the restoration of hair to bald heads by the topical applications of oxidizing substances such as stabilized chlorine dioxide, potassium bromate, or ozone to suppress the enzymatic activity of the reductive enzyme 5-alpha-reductase.

The patent art discloses a number of ways of reducing the growth of human hair as opposed to its conventional removal by cutting, shaving, or depilation. One such method is described in U.S. Patent No. 3,426,137, which pertains to a process for inhibiting the growth of hair by the topical application to a depilated skin area of a composition containing a substituted benzophenone such as 2-amino-5-chloro-benzophenone. Examples in the patent illustrate the reduction of hair growth on the back area of rabbits and on the arm of a male human subject.

Another process for extending the duration of depilation is described in U.S. Patent No. 4,370,315. The process therein comprises the topical application of a composition containing a lipoxygenase along with linoleic acid or derivative thereof. The patent describes the application of such composition to various body parts of female human subjects in the majority of which regrowth of hair was clearly perceptible only after six or more weeks.

In U.S. Patent No. 4,439,432 topical compositions containing progesterone are reported for use in treatment of progesterone deficiency and related conditions, including abnormal hair growth resulting from androgen excess. Further insights on this point

may be obtained from the related literature, among which mention may be made of Simpson et al. "The Effect of Topically Applied Progresterone on Sebum Excretion Rate," Br. J. Derm., Vol. 100, p. 687 (1979), in which progesterone was reported effective in reducing sebum excretion rates in females, but without effect in males. In Goos et al., "An Improved Method for Evaluating Antiandrogens," Arch. Dermatol. Res. Vol. 273, pp. 333-341 (1982), the effect of progesterone on inhibition of hair growth in intact males appears to be doubtful (p. 340, Table 3, Group VI vs. Group X). In Burdick et al., "The Topical Effect of the Antiandrogen Chlormadinone Acetate and Some of Its Chemical Modifications on the Hamster Costovertebral Organ, "Br. J. Derm., Vol. 82, Supplement 6, p. 19 (1970), antiandrogens were either ineffective or of questionable effect in inhibiting flank organ function in normal intact male hamsters. Similarly, in Girard et al., "Inhibition of Testosterone Metabolism and Lipogenesis in Animal Sebaceous Glands by Progesterone," Arch. Dermatol. Res., Vol. 269, pp. 281-290 (1980), progesterone is found effective in the female but not in the male. In all of the above experiments topical antiandrogens were ineffective in males in inhibiting androgenic function. When the female and male responses were compared in both humans and hamsters, only females responded to topical treatment.

In U.S. Patent No. 4,269,831 a substantial reduction in hair growth of the hamster flank organ is among the effects reported from topical application of 17β-hydroxy-17α-propylandrost-4-en-3-one. However reduction in the size of the flank organ is also described, leaving a smaller field on which the hair can grow. Therefore, the reduction in hair growth may be a consequence of a decrease in area of the flank organ rather than an alteration in the character of the hair.

U.S. Patent No. 4,885,289 describes altering

the rate and character hair growth by topical application of 5-alpha-reductase inhibitors and/or cytoplasmic androgen receptor binding agents, while U.S. Patent No. 4,720,489 describes the topical application of ornithine decarboxylase inhibitors for similar purposes, either alone or in combination with the materials of U.S. 4,885,289.

Although it has been theorized that a variety of enzymes are involved in the growth of the cells of human hair, the relationship between such enzymes and between the reactions which they control, as well as their effect upon each other has not been fully understood, as appears from Pegg, Cancer Research, Vol. 48, 759-774 (1988); Gupta et al., Molec. and Biochem. Parasitology, Vol. 23, 247-252 (1987); and Elo et al., Cancer Letters, Vol. 41, 21-30 (1988).

It has now been found that the rate and character of mammalian (including human) hair growth can be altered by topical application to the skin of a composition containing an inhibitor of S-adenosyl-methionine decarboxylase (SAMDC), and further that such an inhibitor can be applied in combination with an ornithine decarboxylase inhibitor to produce greater effects than either inhibitor alone. Compositions containing one or a combination of both inhibitors in any conventional nontoxic dermatologically acceptable carrier or vehicle can be used for application of the combination to the desired areas of the skin. Such compositions may contain 0.1 to 50%, based on the total weight, of an inhibitor of SAMDC, and from 0.1 to 20% of an ornithine decarboxylase inhibitor.

Among the known inhibitors of SAMDC are methylglyoxal bis(guanylhydrazone) (MGBG); diethylglyoxal bis(guanylhydrazone) (DEGBG); and 5'-deoxy-5'-[N-methyl-N-(2-[aminooxy]ethyl)] aminoadenosine (MAOEA).

Among the known ornithine decarboxylase (ODC)

inhibitors which can be used are those described in U.S. Patent Nos. 4,201,788; 4,413,141; 4,421,768; and 4,720,489; of these, the preferred ODC inhibitors are 2-(difluoromethyl)-ornithine(DFMO); alpha-ethynyl ornithine; 6-heptyne-2,5-diamine, and 2-methyl-6-heptyne-2,5-diamine. In choosing ODC inhibitors for use in the practice of this invention, it is important to avoid those known to have secondary pharmacological effects such as 5-hexyne-1,4-diamine, which is known to bring about increases in brain 4-aminobutyric acid levels by a transformation catalyzed by mitochondrial monoamine oxidase. To minimize the risk of alteration of other bodily functions through systemic action, it is preferred to apply the ODC inhibitors in compositions such that the level of application will range from about 1 to about 2000 micrograms of active material per square centimeter of skin; still more preferred is the application of about 50 to about 500 micrograms per square centimeter of skin.

The SAMDC inhibitor or inhibitors is also preferably applied so that the amount of active material is from about 1 to about 5000 micrograms per square centimeter of skin.

The relative proportions of SAMDC inhibitor and of ODC inhibitor in the compositions as applied to the skin is not critical and may be varied over a wide range; preferred are compositions in which the relative proportions range from 1:10 to 10:1 by weight.

The following specific examples are intended to illustrate the nature of the invention without acting as a limitation on its scope.

Example 1

A vehicle or carrier was prepared having the following composition:

Component	Wt. Percent Concentration
Water	68%
Ethanol	16%

Propylene Glycol	5%
Dipropylene Glycol	5%
Benzyl Alcohol	4%
Propylene Carbonate	2%

A series of compositions was prepared each containing a given concentration of specified inhibitor in the foregoing vehicle, as listed in Table 1 below.

Four groups (eight animals in each group) of male intact Golden Syrian hamsters were provided. These animals were considered acceptable models for human beard hair growth in that they display oval shaped flank organs, one on each side, each about 8mm in major diameter, which grow thick black and coarse hair similar to human beard hair. These organs produce hair in response to androgens in the hamster. The flank organs of each hamster were depilated by applying a thioglycolate-based chemical depilatory (Surgex), and to one organ of each animal was applied 10μL. of vehicle alone once a day, while to the other organ of each animal was applied an equal amount of vehicle containing inhibitor. After 14 such applications (Mon.- Fri.) over a period of 18 days, the flank organs were shaved and the amount of recovered hair (hair mass) from each was weighed. The extent of reduction in hair growth by the inhibitor was expressed as the percent decrease in hair mass on the organ treated with inhibitor as compared to the organ treated with vehicle alone. As a control, one group of eight animals had both flank organs of each animal treated with vehicle alone. The results were as shown in Table 1 below.

Table 1

Inhibitor	Flank Organ (mg±SE) Treated	Hair Mass Control	Hair Growth Inhibition (%)
5% MAOEA	2.03±.18	2.68±.13	29.4±5.9
5% MGBG	1.54±.22	2.63.22	40.3±7.4
5% DFMO	0.99±.08	2.89±.22	64.3±3.7

5% MAOEA and 5% DFMO	0.76±.11	2.66±.18	70.9±4.8
None	3.04±.24	3.05±.20	0±.53

Example 2

The same procedure was followed as in Example 1 except that the vehicle used for the compositions consisted of water alone. The compositions used and the results obtained were as shown in Table 2 below:

Table 2

Inhibitor	Flank Organ (mg±SE) Treated	Hair Mass Control	Hair Growth Inhibition (%)
2.5% DEGBG	2.62±.15	3.15±.17	15.9±5.2
5% DFMO	2.70±.22	3.37±.22	18.8±3.7
2.5% DEGBG and 5% DFMO	2.30±.26	2.91±.21	21.7±5.3

Example 3

Compositions were prepared as described in Example 1 containing the inhibitors listed in Table 3. The same test procedure was followed except that the compositions were applied to the hamster flank organs every day for fifteen successive days, at which time hair mass was measured; the results were as follows:

Table 3

Inhibitor	No Animals	Flank Organ (mg±SE) Treated	Hair Mass Control	Hair Growth Inhibition (%)
5% MGBG	6	0.56±.11	0.99+.13	42.3±8.2
5% DFMO	7	0.49±.14	0.92±.13	44.4±18.2
5% MGBG and 5% DFMO	8	0.16±.03	0.87±.08	80.7±3.2
None	7	0.85±.13	0.91±.21	6.47±10.0

Similar results can be obtained with other inhibitors of SAMDC and of ODC.

CLAIMS

1. The process of reducing the rate and altering the character of mammalian hair growth which comprises the step of applying to the skin a composition containing an inhibitor of S-adenosylmethionine decarboxylase.

2. The process as claimed in claim 1, in which said composition contains in addition an ornithine decarboxylase inhibitor.

3. The process as claimed in claim 1 or 2, in which said inhibitor of S-adenosylmethionine decarboxylase is selected from the group consisting of methylglyoal bis(guanylhydrazone), diethylglyoxal bis(guanylhydrazone), and 5'-deoxy-5'-[N-methyl-N-(2-[aminooxy]ethyl)] aminoadenosine.

4. The process as claimed in claim 2, in which said ornithine decarboxylase inhibitor is selected from the group consisting of 2-(difluoromethyl)-ornithine, alpha-ethynyl ornithine; 6-heptyne-2,5-diamine and 2-methyl-6-heptyne-2,5-diamine.

5. The process as claimed in claim 4, in which said inhibitor of S-adenosylmethylthionine decarboxylase is selected from the group consisting of methylglyoxal bis(guanylhydrazone), diethylglyoxal bis(guanylhydrazone), 5' and 5'-deoxy-5'-[N-methyl-N-(2-[aminooxy]ethyl)] aminoadenosine.

6. The process as claimed in any of claims 1, 2, 3, 4 or 5 in which the rate of applying is from 1 to 5000 micrograms of said inhibitor of S-adenosylmethionine decarboxylase per square centimeter of skin.

7. The process as claimed in any of claims 2, 4, or 5 in which the rate of applying is from 1 to 2000 micrograms of said ornithine decarboxylase inhibitor per square centimeter of skin.

8. The process as claimed in claim 7, in which the rate of applying said inhibitor of S-adenosylmethionine decarboxylase is from 1 to 5000 micrograms per square

centimeter of skin.

9. A topical composition for reducing the rate and altering the character of mammalian hair growth comprising a non-toxic dermatologically acceptable carrier and from 0.1 to 50%, based on the total weight of said composition, of an inhibitor of S-adenosylmethionine decarboxylase and from 0.1 to 20% of an ornithine decarboxylase inhibitor.

10. A composition as claimed in claim 9, in which said inhibitor of S-adenosylmethionine decarboxylase is selected from the group consisting of methylglyoxal bis(guanylhydrazone), diethylglyoxal bis(guanylhydrazone), and 5'-deoxy-5'-[N-methyl-N-(2-[aminooxy]ethyl)] aminoadenosine.

11. A composition as claimed in claim 9, in which said ornithine decarboxylase inhibitor is selected from the group consisting of 2-(difluoromethyl)-ornithine, alpha-ethynyl ornithine; 6-heptyne-2,5-diamine and 2-methyl-6-heptyne-2,5-diamine.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/05721

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61K 31/70
U.S.Cl.: 514/46

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.Cl.	514/46

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

CAS, DIALOG SEARCH TERMS: SAMDC INHIBOTOR, ODC INHIBITOR, MGBG, DEGBG, MAOEA, ORNITHINE, DIAMINE

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 4,720,489 (SHANDER) 19 January 1988 See entire document.	1-11
Y	Arch Toxicol, 59 (SUPPL) (9): 455. "Variable Effects of Irritants (Mettylmethacrylate, Tephenyls, Dithranol, and Methylglyoxal -bis- Guanylhydrazone) on the Fine Structure of the Epidermis." 1986. (L. Kanerva et al.) See entire document.	1-11
Y	Acta Dermatovener 62(3):221-224. "Methylglyoxal Bis (guanylhydrazone) and a-difluoro-methylornithine - induced Polyamine Deprivation in in Psoriatic Lesions". 1982 (M. Kousa et al.) See entire document.	1-11
Y	J. Invest, Dermatol 85(6): 518-521. "Regulation of Epidermal Proliferation in Mouse Epidelmis by Combination of Diflouromethyl Ornithine (DFMO) and Merhylglyoxal bis (guanylhydrazone) (MGBG)". 1985. (Abstract 7/5/9). (J.L. McCullough et al.) See entire document.	1-11

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
14 January 1992	03 FEB 1992
International Searching Authority	**Signature of Authorized Officer**
ISA/US	For Diane Gardner NGUYEN NGOC-HO INTERNATIONAL DIVISION

Form PCT/ISA/210 (second sheet) (Rev.11-87)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

Y	J. Invest. Dermatol. 81(5):388-392. "Percutaneous Penetration of Methylglyoxal bis(guanylhydrazone): Effects on Hairless Mouse Epidermis in vivo." 1983. (Abstract 7/5/16). (J.L. McCullough et al.) See entire document.	1-11
Y	Eur. J. Cancer Clin. Oncol. 22(1): 67-67. "Phase I Study of 01 - Difluoromethylornithine and Methyl - Gag." 1986. (T.A.W. Splinter et al.) See entire document.	1-11

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . . . . . because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers . . . . . , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

3. ☐ Claim numbers _____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.